Breaking Through FDA's New "Accelerated" Pathway

Industry specialist speaks about maneuvering through FDA's accelerated pathway.

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For years, FDA's Center for Device and Radiological Health (CDRH) has been criticized for stalling innovation due to long review times. In 2011, CDRH proposed the Innovation Pathway, a priority review program to help breakthrough medical devices reach patients in a timely manner by improving collaboration between FDA and manufacturers and shorten the time and reduce the costs from concept to commercialization for innovative medical devices.

CDRH implemented a formal Priority Review Program (PRP) in 2013. The purpose of the PRP was to establish statutory criteria for granting expedited review to premarket submissions and to outline standard procedures to achieve an efficient expedited review process. Granting priority review status meant that eligible marketing applications were placed at the beginning of the review queue and received additional review resources, as needed.

In April 2015, FDA implemented the Expedited Access Pathway (EAP) program. EAP was a voluntary program based in part on CDRH's experiences with the Innovation Pathway and FDA's experience with programs intended to accelerate the review process for drug products that address unmet medical needs in the treatment of serious or life-threatening conditions. Applications eligible for the EAP program were limited to IDE, PMA and De Novo requests.Both the PRP and EAP programs have now been superseded by the Breakthrough Devices Program (BDP) which was created in response to the 21st Century Cures Act (Cures Act), enacted in December 2016. The Cures Act codified into law the definition and provisions for review of breakthrough devices.

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As with the PRP and EAP program, the BDP is intended to **allow patients more timely access (https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM481588.pdf)** to devices and breakthrough technologies that provide for more effective treatment or diagnosis for life-threatening or irreversibly debilitating diseases, and for which no legally marketed option exists, offers significant advantages over existing alternatives, or the availability of which is in the best interest of the patient.

A comparison of the three programs, presented in Table 1, shows their evolution.

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Vision: Discussion and Collaboration

The BDP is consistent in vision to the EAP program but has been modified based upon the applicable provisions of the Cures Act. Devices granted designation under the EAP program have been automatically incorporated in the BDP. FDA is currently addressing public comments on a draft guidance that was proposed last year[1]. Regardless, the provisions of the

	Priority Review Program (PRP)	Expedited Access Program (EAP)	Breakthrough Devices Program (BDP)
Eligibility	Device that provides for *more effective* treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and meets one of the following criteria: 1. Represents a breakthrough technology, 2. No approved alternatives exist, 3. Offers significant advantages over existing approved alternatives, or 4. The availability of which is in the best interest of the patients.		
Applications Accepted	PMA, DeNovo, 510(k), PDP	IDE, PMA, DeNovo[1]	Q-Sub, IDE, PMA, DeNovo, 510(k)[2]
Interactive Review	No	Yes	Yes
Sr. Management Involvement	No	Yes	Yes
Sprint Discussions	No	No	Yes
Data Development Plan(DRD)	No	Yes	Not mandated
Clinical Protocol Agreement	No	No	Yes
Regular Status Updates	No	No	Yes
When to submit request for designation	At time of marketing application	Included in a Q-Sub, preferably prior to IDE pivotal study.	Before submission of a marketing application. Requests should be made in a separate Q-Sub
FDA timeframe for granting/rejecting request	• 510(k) or DeNovo = 14 days within receipt of submission • PMA: during the 45 days filing review	Within 30 days of receipt[3]	Within 60 days of receipt
Review TIme	Eligible applications will be placed at the beginning of the review queue. PRP applications reviewed on a first-in/first-reviewed basis.	PMAs with EAP designation receive Priority Review. De novo requests with EAP designation - FDA intends to make a determination in less than 120 days	Same as PRP

[1] Not all provisions of the EAP are applicable to DeNovo applications.
[2] Includes combination products under the device pathway.
[3] If there is insufficient information for FDA to make a decision, FDA may request the sponsor submit additional information. If additional information is not received within 30 days, FDA may reject the request

BDP are already effective per the Cures Act.

Unlike the EAP, which only allowed IDE, PMA and De Novo applications, the BDP also applies to Q-submissions (Q-Sub), Investigational Device Exemptions (IDE) and 510(k) premarket notifications. Furthermore, combination products under the device pathway are also eligible for BDP.

FDA cautions however that combination products may raise unique scientific and regulatory challenges. As a result, it may not be possible to apply all the policies of the BDP to combination products that receive Breakthrough designation. Challenges associated with coordinating review with a different Center must also be considered.

Both the EAP and BDP offer manufacturers the opportunity for interactive review with involvement from senior management. One new feature of the BDP is "sprint" discussions. Sprint discussions are offered with the goal of reaching agreement on a specific topic within a time-period proposed by the sponsor and agreed by FDA. The number and format of sprint discussions may vary based on project needs.

Unlike with Q-Subs, the information and proposals to be discussed during the sprint discussion may be modified during the sprint discussion as agreed upon with FDA. Points of disagreement that cannot be resolved quickly are expected to be expeditiously elevated to senior management. In addition to sprint meetings, FDA and sponsor may agree to regular status updates on the progress of Breakthrough device applications. These updates will provide an opportunity for a high-level view of the project and identification of potential hurdles.

Support for Data Development

With the BDP, sponsors may request coordination and early agreement from FDA on a Data Development Plan (DDP). The DDP is a high-level document that describes how the company will balance premarket non-clinical and clinical data with, as applicable, post-market clinical data. The DDP was a requirement in the EAP program. A number of companies have found the interaction with FDA during the DDP process quite helpful, while other companies found it to be burdensome. One company, in particular, who was granted EAP designation but chose to remain anonymous, found the EAP program to be a "major disappointment" due to the lack of FDA interaction during the DDP process.

Though the company was accepted into the program, FDA never assisted them in developing a DDP. According to the company, the Agency deflected from the EAP guidelines and instructed the company to go through the Pre-Submission instead. Ultimately, the company pulled out of EAP. Under the new BDP, FDA's review of a DDP follows the same model as the sprint discussion described above, which is expected to alleviate such burdens.

According to Maureen Dreher, Ph.D. a policy analyst with CDRH, "[FDA has] found that sponsors of devices granted Breakthrough status need different types of support in determining the best way to utilize the opportunities that the program offers.. With those needs in mind, the program was designed with significant flexibility. For example, devices granted Breakthrough designation prior to human clinical experience may need more support on non-clinical testing issues while those designated after a feasibility study may need more support defining an efficient design for a pivotal trial."

Products in the Pipeline

Between April 13, 2015 through April 30, 2018, FDA received and rendered decisions on 115 requests for Breakthrough designation. Of those, 70 were granted, with only a "handful" of submissions granted marketing authorization. This includes devices from the EAP and new BDP. While this may seem trivial, especially since the EAP program has been in place for more than three years, Dreher explains that, "When a designation is granted, the device can

be relatively early in its development or under investigation in a human clinical study, which may be a feasibility study. Therefore, this handful of marketing authorizations is expected to increase in the next few years as more designated devices in the pipeline enter more advanced stages of development."[2]

One of the few success stories that came out of the EAP was IDx's AI-based device for the autonomous detection of diabetic retinopathy (i.e., IDx-DR). IDx explained via email that over their seven-year development process, they had numerous interactions with the Agency, who informed them of BDP. IDx submitted a request for inclusion and FDA granted EAP designation shortly after. The company stated: "While the process was long, we would not be the same company without the guidance and feedback that we were fortunate to receive from the FDA." For IDx, the BDP proved beneficial as they found the review timeline significantly quicker than expected. IDx submitted a De Novo application on January 12th and received approval on April 11th.[3]

Faster Decisions

It is not clear at this stage if the new BDP will result in shorter approval times as IDx experienced. Expectations within industry are mixed; some companies believe that the changes made to the EAP are not sufficient to ensure faster decisions from FDA, while remain positive. The consensus is that FDA's intentions are good; however, some believe FDA is conflicted since there is no internal incentive for them to approve products with less data. In the spirit of MDUFA, which imposed review time performance goals for FDA in exchange for user fees, one suggestion would be to set a performance goal for agreement on the DDP. The DDP has been identified as one of the main hurdles with the EAP. As part of the BDP, FDA now offers "sprint" meetings, which can be used to facilitate decisions on the DDP. However; there are no concrete timeframes for sprint meetings. By treating the DDP as a separate submission with a set review time it incentivizes FDA to make faster decisions, which will help companies "break through" the new BDP.

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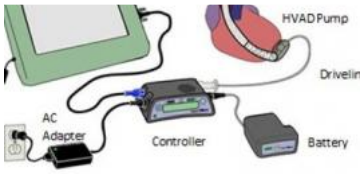

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